Title of Study: Using Virtual Reality (VR) Models for Preoperative Planning
Technology Provider: Ceevra, Inc.
Device Name: Ceevra Reveal

I. BACKGROUND AND RATIONALE

a. Introduction

The purpose of the proposed study is to assess whether surgeons who view virtual reality (VR) models of their patients' anatomy during the preoperative planning process develop a better understanding of such anatomy, resulting in more efficient operations and improved patient care.

b. Study justification and design

The typical approach for a surgeon planning an operation such as a robotic assisted laparoscopic partial nephrectomy (RALPN) involves reviewing a traditional CT scan or MRI, which is comprised of a series of 2D black and white slices that the surgeon then views from multiple angles to form a "mental 3D reconstruction" of the kidney, the mass, and any important structures near the kidney. Surgeons are continuously looking for ways to improve upon this planning process and enhance patient care, and one emerging area for such improvement is the use of advanced imaging technologies.

In this study, three-dimensional (3D) models of the patient's anatomy will be created by technology provider Ceevra, Inc. ("*Ceevra*") using software that converts preexisting CT scans and MRIs into 3D models and then displays those models in a virtual reality format (the "*VR Models*") through mobile phones or tablets. The software utilized by Ceevra to perform these functions, Clarity Reveal, is classified as a medical device, product code LLZ (Image Processing System) (the "*Device*"). On August 3, 2017, Ceevra received 510(k) clearance from the FDA (registration number K171356) for the use of the Device for preoperative surgical planning. On July 20, 2018, Ceevra received additional 510(k) clearance from the FDA (registration number K173274) for the use of the Device to display the VR Models during the operations as well. The indications for use are as follows:

> Ceevra Reveal 2.0 is intended as a medical imaging system that allows the processing, review, analysis, communication and media interchange of multi-dimensional digital images acquired from CT or MR imaging devices. It is also intended as software for preoperative surgical planning, and as software for the intraoperative display of the aforementioned multi-dimensional digital images. Ceevra Reveal 2.0 is designed for use by health care professionals and is intended to assist the clinician who is responsible for making all final patient management decisions.

In the VR Models, each primary anatomical structure (for example, the kidney, the kidney mass, the main renal vein and the main renal artery) is assigned a unique color and texture to help surgeons identify these structures. The kidney is made translucent to enable the surgeons to see the depth of the mass as well as its size and shape. The VR Models will be

accessed by surgeons through their mobile phones, and then viewed through a generally commercially available VR headset to allow for a more immersive viewing experience.

The surgeons involved in this study will view both the VR Models and the original CT/MRI during their surgical planning process. The surgeons may also view the VR Models and the original CT/MRI during the operation itself. The researchers will then compare the results of the operations in which both the VR Models and the CT/MRIs are viewed to the results of operations in which the same surgeons viewed only the CT/MRIs. As more fully detailed Exhibits A and C below, endpoints to be evaluated include intraoperative times (specifically, tumor localization, tumor resection, reconstruction), blood loss, clamp time, patient hospital stay, margins and complications.

The researchers hypothesize that viewing the VR Models during the preoperative planning process may enable the participating surgeons to develop a better understanding of their patients' anatomy, which in turn may have the following benefits:

- Improved surgical efficiency, for example reduced operating time and associated time under anesthesia; reduced blood loss; and reduced ischemia; and
- Improved patient recovery process, including reduced post-operative discomfort and shortened hospital stay.

c. Prior similar studies

In 2016, Dr. Joseph Shirk undertook a limited study at UCLA Health pursuant to an IRB-approved quality assurance waiver. Using several off-the-shelf software applications, Dr. Shirk created virtual reality models from CT scans for 30 upcoming RALPN cases. During the preoperative planning process for those cases, the surgeons viewed both the source CT scan as well as the virtual reality model. Using multivariate statistical analysis, the results of those cases were compared to 30 RALPN cases performed by same surgeons in which only the underlying CT/MRI was viewed during the preoperative planning process. The endpoints and results of this study were as follows:

- Operative time (30% reduction when VR Model used during preoperative planning)
- Blood loss (51% reduction when VR Model used during preoperative planning)
- Ischemia (25% reduction when VR Model used during preoperative planning)
- Patient hospital stay (20% more likely to be discharged by post-op Day 2 when VR model used during preoperative planning)
- Case complexity (27% higher average Nephrometry score for cases in which VR model used during preoperative planning)

The researchers in this study seek to expand significantly on the above described study by including new primary endpoints and utilizing VR Models created by Ceevra with the Device.

d. Relevant Literature and Data

The prior study described above represents the first study to demonstrate a definitive advantage in surgical planning using virtual reality models. Furthermore, the study demonstrated that the surgeons in the study were more willing to perform surgery on complex tumors with the VR models.

Previous studies using 3D printed models have shown subjective improvement in operative planning when surgeons were surveyed after viewing the models (Zhang et al, 2016), but review of this technique is limited (Soliman et al, 2015). VR models provide an increased level of detail beyond what is seen in 3D printed models, since the fidelity of 3D printing limits detail.

Advanced imaging technologies such as CT or MRI guided biopsy also differ markedly from this study, as they rely on fusion of multiple imaging modalities as well as the use of intraoperative imaging.

II. CASE TYPES INVOLVED IN STUDY

a. Robotic assisted laparoscopic partial nephrectomy (RALPN)
b. Exclusions:
    i. Cases involving subjects who are minors, pregnant or require an authorized representative for informed consent
    ii. Cases in which the subject has a solitary or horseshoe kidney
    iii. Cases in which the subject has more than two masses in the applicable kidney
    iv. Cases involving a bilateral operation

III. **STUDY ENDPOINTS.** The Primary and Secondary Endpoints are described on **Exhibit A**. For both the Control Cases and the Intervention Cases (as such terms are defined in Section IV below):
a. All Primary Endpoints (except Total Operative Time) will be measured by review of the video case recording; and
b. All Secondary Endpoints and Total Operative Time will be measured using data derived from the EHR.

IV. STUDY DURATION, CASES AND STATISTICAL MODEL

a. Study Duration

This study will commence as soon as practicable following IRB approval, and will end on the earlier of (i) the date on which all Intervention Cases have been performed, as more fully detailed below, and the researchers have completed all associated statistical analysis or (ii) March 31, 2019.

b. Intervention Cases

The set of intervention cases ("*Intervention Cases*") will be all operations:

- That meet the criteria set forth in Section II above;
- Are performed by the surgeons participating in the study;

- Which occur after commencement of the study, until such time as the calculated number of Intervention Cases (as discussed more fully below) have been completed; and
- Which are identified Intervention Cases as discussed in subsection (d) below.

The calculated number of Intervention Cases is set forth on **Exhibit A**. approach used to calculate such number is detailed in subsection (d) below (Randomization, Blinding and Sample Size Calculation)..

Interims computations of sample size will be performed to ensure the study maintains 70% power to detect a 10% difference in the primary endpoint with use of the appropriate statistical test. An interim computation will occur when ½ of the cases have completed the protocol. The interim computations 1) will involve only interim estimates of standard deviations of interest along with their corresponding 95% confidence intervals, 2) will be blind to whether "Group 1" or "Group 2" was to the VR-aided method, and 3) will not reveal to the surgeons or patients any information about magnitudes of group differences. If power is deemed inadequate, the sample size will be adjusted in both the number of Control Cases and Intervention Cases accordingly. This will be accomplished by repeating the sample size calculation described in Section IVd with data from the ongoing study. Adjustments to sample size are anticipated to be relatively small in relation to the large overall sample size.

c. Control Cases

The set of control cases ("*Control Cases*") will be all operations:

- That meet the criteria set forth in Section II above;
- Are performed by the surgeons participating in the study;
- Which occur after commencement of the study, until such time as the calculated number of Control Cases (as discussed more fully below) have been completed; and
- Which are identified as Control Cases as discussed in subsection (d) below.

Sample size for Intervention Cases has been calculated based on the methodology described above, and Control Case sample size shall be calculated using a 1:1 group ratio.

d. Randomization, blinding, and sample size calculation

Eligible subjects identified from the medical record will be those who are 1) scheduled to undergo RALPN surgery, 2) willing to consent to the surgery being performed by one of the four surgeons participating in the study, and 3) willing to be assigned by randomization to a preparation method (VR-aided or control). Each case will be assigned to one of the two preparation methods by a randomization procedure that is stratified by surgeon (four separate surgeon-specific randomization schedules.) Each surgeon-specific randomization schedule will be prepared using permuted blocks of size 2; i.e., each 2-patient block will be some permutation of {VR-aided, Control}. Thus, each surgeon's cases will be randomized in a 1:1 ratio. Use of permuted blocks thus avoids any confounding of preparation method with temporal trends (e.g., trend due to a learning curve.) Approximately 20 sequentially numbered opaque sealed envelopes (SNOSEs) will be prepared for each individual surgeon, each containing the treatment assignment for one case, and will provided to the Research Coordinator. The treatment code will remain concealed inside the envelope until

the moment the case is ready to be prepared. Patients, personnel gathering data from the video review, and statistician will be blinded. Control and intervention groups identifiers will be known only to the research personnel opening the sealed envelope for random group assignment and extracting patient data from the electronic medical record.

We calculated the sample size based on our pilot data of the total operative time, which shows an effect size of 0.44 regarding the difference of total operative time between VR-aided and control groups. We took the within-surgeon correlation to be 0.3. We use data from the most-of-interest variable (aka total operative time). To account for the within-cluster correlation, we adopted the sample size calculation method proposed in [1]. We took three values of within-cluster correction (rho = 0.3, 0.5, 0.7) to consider low/moderate/high levels of within cluster correlation. In order to account for multiple endpoints and some other unpredictable factors, we propose to raise the sample size by 15%. We selected rho=0.3 given the wide variation in case complexity seen in our pilot study, which drastically limited within-cluster clustering. Our target sample size using this method is 78 patients.

	rho = 0.3	rho = 0.5	rho = 0.7
Before adjustment	34	39	47
After 15% adjustment	39	45	54

[1] Diggle, P. J., Heagerty, P., Liang, K. Y., and Zeger, S. L. (2002). Analysis of Longitudinal Data. New York: Oxford University Press.

e. Statistical Model

Baseline values (means, standard deviations and proportions) will be tabulated together with corresponding confidence intervals (CIs) for each primary endpoint in both the Control Cases and Intervention Cases based on relevant historical data. For primary endpoints of various operative times, the nonparametric Wilcoxon signed rank test will be utilized to calculate the sample size needed to have 70% power to detect a 10% difference. False Discovery Rate (FDR) control will be enforced by using Benjamini-Hochberg procedure at the level of 5% in order to account for multiple testing issue.

Statistical analysis will include standard comparison of baseline endpoints between VR-aided and control groups with the appropriate statistical tests depending on the type of outcomes. For continuous outcomes (e.g. various operative times), the nonparametric Wilcoxon signed rank test will be used for comparison, which does not rely on the normality assumption. For binary outcomes (e.g. Mortality), Fisher's exact test will be used. P-values of all tests will be reported. The threshold of rejecting null hypothesis will be chosen at the conventional level of 0.05. Tests fail to be rejected will be reported as inconclusive. To study the adjusted difference between case/control group, we will also use generalized linear mixed model to regress the endpoint variables on Surgical and Clinical covariates listed in **Exhibit A,** where random effects will be imposed on surgeon clusters. Depending on the type of outcome, the linear mixed model (for continuous outcome) or the logistic mixed model (for binary outcome) will be used. To ensure normality, the continuous outcome will be Box-Cox transformed. In the regression analysis, we also use model diagnosis tools, such as QQ-plots to ensure various assumptions for the regression model are met. In

addition, to test the reliability of our model, we will also perform sensitivity analyses by splitting data into training and test set and perturb various assumptions (such as normality assumption and the Box-Cox transformation) in the regression model and inspect how well the results can be reproduced. The repeated measure ANCOVA will be used to test the adjusted difference between case/control groups.

V. SURGEON SURVEYS

a. **Post-Operative Surveys**: A short survey will be administered to the surgeon following completion of each Intervention Case ("*Post-Operative Surveys*"). The survey will include questions regarding the Primary Endpoints (as measured on a Likert-type scale), and the helpfulness of the VR Models during case planning. No PHI will be reflected or gathered in these surveys.
b. **Surgeon Experience Surveys**: Surgeon experience surveys will be administered with each participating surgeon two times during study: The first one after the surgeon has completed 5 Intervention Cases, and the second one at the completion of the study ("*Surgeon Experience Surveys*"). No PHI will be gathered or reflected in these surveys. Initial list of questions set forth on **Exhibit B**.
c. **Purpose**. The Post-Operative Surveys and Surgeon Experience Surveys will be used by the researchers to further assess whether and to what degree the VR Models:
    i. Impact the surgeons' understanding of their patients' anatomy;
    ii. Impact the surgeons' confidence in their preoperative plans;
    iii. Impact the surgeons' accuracy in their preoperative plans;
    iv. Impact the surgeons' efficiency in their intraoperative execution;
    v. Are perceived as particularly beneficial in cases with any specific anatomical characteristics;
    vi. Are perceived as particularly beneficial to any specific surgery types; and
    vii. Are perceived as more or less helpful when viewed in VR format as opposed to regular 3D format.

VI. HOSPITAL PARTICIPANTS AND RESPONSIBILITIES

a. Principal Investigator (PI)
    i. Overall point person for study.
    ii. Coordinates support for study with other participants, including Research Coordinator and surgeon users.
b. **Research Coordinator ("RC"):**
    i. Identify, collect and manage:
        - The CTs and MRIs from which the VR Models will be created by Ceevra
        - Data regarding Control Cases ("***Control Case Data***") and Intervention Cases ("***Intervention Case Data***")
    ii. Deidentify each source CT/MRI using deidentifying software (or ensures that Radiology deidentifies the image prior to delivery to the RC); deliver the deidentified image to Ceevra along with a unique identifier.
    iii. Coordinate with surgeon users to ensure that both the VR model and the underlying CT/MRI are reviewed prior to operation.

iv. Assist with administration of the Post-Operative Surveys and the Surgeon Experience Surveys.

c. Surgeon Users. Key activities:

i. Identify upcoming cases for which VR models will be created.
ii. Oversee receipt of informed consents from all patients participating in the study.
iii. Provide the mobile phone used for viewing the VR models (Ceevra to provide VR headsets, 1 per surgeon user).
iv. Before each Intervention Case operation, review the source CT/MRI and then review the associated VR Model for purposes of case planning.
v. Participate in Post-Operative Surveys and Surgeon Experience Surveys.

VII. PROJECT IMPLEMENTATION

a. Protocol for Case Data. Control Case Data and Intervention Case Data will be will be extracted from the EHR system, and the Post-Operative Surveys. It will be tracked via two forms maintained within REDCap which requires unique user IDs and passwords:

i. First form will include patient information (listed below) and a unique identifier. This form will be accessible by researchers only.
    1. Medical Record Number (MRN)
    2. Surgeon Number
    3. CT/MRI ID #
    4. Operation Date
    5. Unique Identifier
ii. Second form will include the unique identifier and outcomes data, but no PHI. See **Exhibit C** for example of data fields (partial nephrectomy cases). This form will be accessible by both site and Ceevra researchers.

b. Protocol for Control and Intervention Cases and Randomization

i. For Intervention Cases, surgeons will be provided with the VR model to view prior to the operation in addition to the CT or MRI scan as described below. For Intervention Cases, surgeons will also have the option to view the VR model during the operation in addition to the CT or MRI scan. For Control Cases, surgeons will view the CT or MRI scan only.
ii. Subjects will be identified from the medical record as scheduled to undergo one of the surgery types being included in the study, with the surgery being performed by one of the surgeons participating in the study. Subjects will be randomized at a 1:1 ratio to either control or intervention groups using block randomization.

c. Protocol for VR Models

i. PI/RC identifies upcoming Intervention Cases, based on the above criteria and the results of randomization, for which VR models are to be created.
ii. PI/RC obtains source CT/MRI for such cases, deidentifies the same using deidentifying software (or ensures that Radiology deidentifies the image prior to delivery to the PI/RC), delivers it to Ceevra along with a unique identifier.

iii. Ceevra creates VR model from the deidentified CT/MRI. Once completed:
- Delivers VR Model back to PI/RC, along with the unique identifier.
- Notifies applicable surgeon user (with copy to PI and RC) that VR Model is available for viewing through the mobile app.

iv. Prior to operation for Intervention Cases, PI/RC contacts applicable surgeon user to ensure viewing of both the VR Model and the underlying CT/MRI.

d. Data Management Plan. Information regarding the Intervention Cases and Control Cases will be collected and analyzed, as detailed below. PHI will be reviewed during the study as necessary to identify potential participants with specified medical conditions, and a separate HIPAA authorization form will be obtained from patients. However, no PHI will be shared outside of the site.

i. *Medical Images*: CTs and MRIs will be obtained from the hospital PACS system. All PHI will be removed from the images prior to sharing them with Ceevra.

ii. *Case Data*: Intervention Case Data and Control Case Data will be extracted from the electronic video data, the hospital EMR system, and surgeon surveys to be administered following the operations. The case data will be tracked via the REDCap forms described above in Section VIII(b). The case data from the hospital EMR system will be entered into the applicable form by a researcher (other than the PI), and the results of the surgeon surveys may be entered into the applicable form either by a Ceevra researcher or a researcher (other than the PI).

iii. *Data Quality*. REDCap forms will be configured to validate data fields at the time of entry to ensure the completeness and validity of data. REDCap locking and signing features will be employed to ensure record-level completeness.

iv. Data Security and Integrity. REDCap employs secure authentication features to prevent unauthorized access to trial data. REDCap authorization features will be employed to ensure that form and data access is limited to the personnel with a need to access them. Additionally, REDCap data management mitigates the possibility of lost or corrupt data. REDCap audit trails provide the ability to verify the above, if needed.

v. *Data Management and Data Computations*. Data management will be overseen by the RC. Data computations will be performed by the Biostatistician.

VIII. TRAINING, MEASURING & COMMUNICATING

a. Training with surgeon users on accessing/using mobile app and VR Models. Each surgeon will be trained either in person or via video call. During the training, the surgeon will be trained how to access the VR models from their mobile phones and how utilize several viewing features such as showing/hiding anatomical parts; zooming in/out on the model; and viewing the model in VR mode.
b. Kickoff Meeting (in-person meeting at medical center):
    i. Introduce participants
    ii. Outline study processes, timeline and objectives
c. Bi-Weekly Assessments
    i. Data for cases involving the VR Models will be reviewed in a bi-weekly basis to assess whether there are any more or different issues in cases in which the VR Models were used during preoperative planning and, if so, whether any such differences can be attributed to the VR Models.
    ii. In the event any unexpected adverse event occurs in a case in which a VR Model is used, the study will be immediately suspended until a determination is made whether such event is attributable to the VR Model. If such determination is affirmative, then the researchers will assess whether to continue or discontinue the study based on a number of factors including but not limited to the magnitude of the adverse event, the feasibility of preventative measures, and the likelihood of its recurrence after implementation of any such measures.
d. Surgeon Experience Surveys (2x during study per surgeon)
e. Study Conclusion Meeting (in-person): Final study results

EXHIBIT A
COVARIATES, ENDPOINTS AND SAMPLE SIZE BY SURGERY TYPE

		Robotic Assisted Laparoscopic Partial Nephrectomy
Surgical Covariates	**Unit**	
Surgeon Experience Level	Years	✓
Surgeon Identifier	Number	✓
Resident Involvement	Yes/No	✓
Fellow Involvement	Yes/No	✓
Clinical Covariates	**Unit**	
Age	Years	✓
Sex	M/F	✓
Charlson Comorbity Index	NA	✓
Nephrometry Score	NA	✓
Mass Size	CM	✓
Mass Location	Segment	
Laterality	R/L	✓
Primary Endpoints	**Unit**	
Hilum Dissection	Minutes	✓
Hepatic Vessel Dissection	Minutes	
Tumor Localization	Minutes	✓
Tumor Resection	Minutes	✓
Reconstruction Time	Minutes	✓
Total Operative Time	Minutes	✓
Secondary Endpoints	**Unit**	
Blood Loss	cc	✓
Clamp Time	Minutes	✓
Warm Ischemia Time	Minutes	
Pringle Time	Minutes	
Conversion to Open	Yes/No	✓
Conversion to Radical	Yes/No	✓
Conversion from Wedge to Glissonian	Yes/No	
Intraoperative Complication	Yes/No	✓
Mortality	Yes/No	✓
Patient Hospital Stay	Days (post-op)	✓
Positive Margin	Yes/No	✓
Post-Op Complications	Yes/No	✓
Readmissions	Yes/No	✓
Intevention Case Sample Size		
		39

EXHIBIT B
SURGEON EXPERIENCE SURVEY QUESTIONS

1. How likely are you to recommend the VR Models to other surgeons in your department (scale 0-5, with 0 being “I would recommend against use of the VR Models”; 1 being “I am not ready to make any recommendation”; and 5 being “I would definitely recommend the VR models to other surgeons in my department”)
2. How would you rate the “imaging quality” of the VR model. For imaging quality, consider aspects such as detail, resolution, color, translucency (scale 0-5, with 1 being Very Poor and 5 being Excellent).
3. How would you rate the “viewing experience” of the VR model. For viewing experience, consider elements such as depth, angle, ability to rotate model, ability to zoom in/out, ability to show/hide anatomical parts. Same answer scale as Question 2.
4. How much did the VR model impact your confidence in your pre-operative surgical plans. (scale 0-5, with 0 being “Using the VR Model made me feel less confident” and 5 being “Using the VR Model made me feel significantly more confident”)
5. How much did the VR model improve your understanding of the patient’s anatomy. (scale 0-5, with 0 being “The VR Model did not improve my understanding of the patient’s anatomy or was confusing” and 5 being “The VR Model significantly improved my understanding of the patient’s anatomy”)
6. What did you like best about the VR model as compared to the CT/MRI (Choices: I did not like any aspects of the VR model; ease of access/viewing from mobile phone; imaging quality; viewing experience; ability to see entire operating site in one view vs. multiple views axial/coronal/sagittal; other)
7. What recommendations do you have for improving the VR models or the viewing experience.
8. Please identify any key anatomical parts that you feel are missing from the model.
9. How helpful is accessing and viewing the image from your own mobile phone or tablet (as compared to viewing images from computer or workstation) (scale 0-5, with 0 being not very helpful and 5 being extremely helpful)
10. How helpful is viewing the image in Virtual Reality mode (as compared to viewing image in regular 3D mode) (scale 0-5, with 0 being “It was less helpful to view the image in Virtual Reality Mode than it was to view it in regular 3D mode” and 5 being “It was extremely helpful to view the image in Virtual Reality mode as opposed to only viewing it in regular 3D mode”)
11. If you answered 0 or 5 to Question 10, provide detail as to why.

EXHIBIT C

EXAMPLE CASE OUTCOMES DATA FIELDS

Outcomes Data categories for Partial Nephrectomy:

- Preoperative parameters
  - Age
  - Sex
  - Race
  - 1 or 2 kidneys
  - Kidney side (R vs L)
  - Tumor size (cm)
  - Tumor location (upper, lower, middle pole)
  - Tumor orientation (anterior or posterior)
  - Percentage of tumor protruding (% endophytic)
  - Tumor density (% solid)
  - Nephrometry score, with modifier for multiple tumors
- Surgical technique
  - Case type (robotic partial)
  - Surgical approach (transperitoneal; retroperitoneal)
  - 4^{th} Robotic arm used (y/n)
  - Arteries clamped (0-4)
  - Veins clamped (0-4)
  - Ultrasound used (y/n)
  - Firefly used (y/n)
- Case Outcomes
  - Tumor localization time
  - Tumor resection time
  - Reconstruction time
  - Total operative time
  - Blood Loss (cc)
  - Clamp time (mins)
  - Conversion to open (y/n)
  - Conversion to radical (y/n)
  - Operative complication (y/n)
- Post-op Outcomes
  - Hospital stay (days)
  - Positive margins (y/n)
  - Post-op complication
  - Readmission